UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:			
John Ong et al.		Art Unit:	1654
Appln. No.:	10/559,595	Examiner:	HA, Julie
Filed:	November 30, 2005	Atty. Docket:	0501US-UTL1
For:	*Novel Methods and Compositions for Enhanced Transmucosal Delivery of Peptides and Proteins*	Confirm. No.:	2750

APPEAL BRIEF

Commissioner for Patents
Mail Stop Appeal Brief
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

In response to the final Office Action dated February 20, 2009 and subsequent to the Notice of Appeal filed on May 20, 2009, Applicants submit the following Appeal Brief.

CERTIFICATE OF TRANSMITTAL UNDER 37 C.F.R. 1.8

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being electronically filed via EFS-Web at the United States Patent and Trademark Office, on the date shown below.

7/17/09
Date of Deposit

Marutzella Castro

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Real Party in Interest

The real party in interest in the case is Amylin Pharmaceuticals, Inc., the assignee of record.

Related Appeals and Interferences

There are no other appeals or interferences related to this case.

Status of the Claims

Claims 1-10 and 15-34 are pending and under appeal. Claims 11-14 and 35-50 are canceled.

Status of Amendments

An amendment was filed after final rejection, on May 20, 2009. The amendment canceled claims 11-14 and 35-50 and was entered.

Summary of Claimed Subject Matter

The present invention provides a pharmaceutical composition for the transmucosal administration of a bioactive peptide or protein of interest (specification, p. 3, lines 8-9). The composition comprises a bioactive peptide or protein of interest, a cationic polyamino acid, and a compatible buffer (specification, p. 3, lines 8-11). In one embodiment the bioactive protein or peptide is an exendin (p. 4, lines 14-15), the cationic polyamino acid is poly-arginine (p. 5, line 2), and the compatible buffer is glutamic acid (p. 3, line 21). The compatible buffer does not cause precipitation of the cationic polyamino acid at the pH of the composition (specification, p.

3, lines 10-12). The buffer has a mono-anionic or neutral net charge (specification, p. 3, lines 11-12). The bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition (specification, p. 8, lines 16-17). The transmucosal absorption of the bioactive peptide or protein is increased relative the absorption of said bioactive peptide or protein in the absence of said cationic polyamino acid (specification, p7, lines 16-21).

According to claim 22, the present invention provides a pharmaceutical composition for transmucosal administration of a bioactive peptide or protein of interest (specification, p. 3, lines 8-9). The composition comprises about 0.01% to about 5.0% (w/v) of said bioactive peptide or protein of interest (specification, p. 4, lines 31-32); about 0.01% to about 1.0% (w/v) of a cationic polyamino acid having a molecular weight between about 10 kDa and about 200 kDa (p. 4, line 34 – p. 5, line 2); and about 0.01% to about 10.0% (w/v) of a compatible buffer (p. 5, line 3), wherein at a pH of between about pH 4.0 and about 5.0, said compatible buffer does not cause precipitation of the cationic polyamino acid and has a mono-anionic or neutral net charge (p. 5, lines 3-5). The bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition (p. 8, lines 16-17). The transmucosal absorption of the bioactive peptide or protein is increased relative the absorption of said bioactive peptide or protein in the absence of said cationic polyamino acid (p. 7, lines 21-24).

With respect to claim 27, the invention provides a pharmaceutical composition for transmucosal administration comprising about 0.5% (w/v) of exendin-4; about 0.5% (w/v) of poly-arginine having an average molecular weight of about 141 kDa; and about 0.56% monosodium glutamate monohydrate (w/v), at a pH of about 4.5 (p. 5, lines 8-12). The exendin-4 has the same net charge as the poly-arginine at the pH of the composition (p. 8, lines 16-17).

With respect to claim 31, the invention provides a pharmaceutical composition for transmucosal administration comprising about 0.5% (w/v) of exendin-4; about 1.0% (w/v) of poly-arginine having an average molecular weight of about 141 kDa; and about 0.56% monosodium glutamate monohydrate (w/v), at a pH of about 4.5 (specification, p. 5, lines 13-17). The exendin-4 has the same net charge as the poly-arginine at the pH of the composition (page 8, lines 16-17).

Grounds of Rejection to be Reviewed on Appeal

1. Whether claims 1-10 and 15-34 are unpatentable under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

2. Whether claim 1 is unpatentable under 35 U.S.C. 102(b) over Rothbard et al. (US 2002/0009491).

3. Whether claims 1-4, 6-7, 9-10, 15-16, and 18-21 are unpatentable under 35 U.S.C. 102(a) as being anticipated by Defelippis et al. (WO 02/098348).

4. Whether claims 1-4, 6-7, 9-10, 15-16, and 18-21 are unpatentable under 35 U.S.C. 102(e) as being anticipated by Defilippis et al. (WO 02/098348).

5. Whether claims 1-10 and 15-26 are unpatentable under 35 U.S.C. 103(a) as being obvious over Young et al. (US 2003/0087820) in view of Baichwal (USP 5,330,761) and Ryser (USP 4,847,240).

Argument

35 U.S.C. 112, second paragraph

This rejection will be discussed first because it informs the remaining rejections.

A claim is indefinite if one skilled in the art would understand the bounds of the claim when read in light of the specification. *Invitrogen Corp. v. Biocrest Mfrg, L.P.*, 424 F.3d 1374 (Fed. Cir. 2005). If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, the demands of 35 U.S.C. § 112 are satisfied. *Credle v. Bond*, 25 F.3d 1566; 30 USPQ2d 1911 (Fed. Cir. 1994).

Claims 1-10 and 15-34 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention (final Office Action mailed 1/20/09, p. 15).

The rejection alleges that it is unclear how a bioactive peptide or protein of interest will have the same net charge as the cationic polyamino acid. The rejection alleges that if the poly-arginine were a 13mer, this would give a net charge of +13 and it is unclear how a bioactive peptide or protein, such as exendin-4, could have a net charge of +13 (final Office Action mailed 1/20/09, p. 15, line 18 – p. 16, line 6).

It is important to properly interpret the meaning of the claim. Claim 1 recites that the bioactive peptide or protein of interest has the "same net charge" as the cationic polyamino acid at the pH of the composition. It appears that the rejection is not based on a proper interpretation of this claim term.

It is well established that the claims must be read in view of the specification, of which they are a part. *Markman v. Westview Instruments, Inc.* 52 F.3d 967; 34 USPQ2d 1321 (Fed. Cir. 1995) (in banc) *aff'd*, 517 U.S. 370; 38 USPQ2d 1461 (1996) *Bell Comm. Res., Inc. v. Vitalink Comm. Corp.*, 55 F.3d 615, 620; 34 USPQ2d 1816, 1819 (Fed. Cir. 1995). Thus, the meaning of the term "same net charge" used in the claims must be informed by the specification. Paragraph 23 of the specification clearly indicates that "same net charge" refers to the overall positive or negative charge, and not the magnitude of the charge. Paragraph 23 of the specification (p. 8, lines 16-20) states:

> "In one embodiment the peptide or protein has the same net charge as the polyamino acid at the pH of the composition. For example, at the pH of the composition both the protein the bioactive peptides or protein and the polyamino acid have a net positive charge. In this situation, it is not necessary that the magnitude of the charge be identical, but only that the net charge be the same." (emphasis added)

When the claims are properly interpreted in view of the specification and using proper legal precedent, it is clear that the claims are not indefinite.

The rejection also refers to claim 31, referencing the claim term "...wherein the exendin-4 has the same net charge as the poly-arginine at the pH of the composition." The rejection alleges that it is unclear how a bioactive peptide or protein of interest will have the same net charge as the cationic polyamino acid (Office Action mailed 1/20/09, p. 17, lines 18-22). It is

noted that the pH recited in claim 31 is 4.5, at which pH the charged groups such as arginine, lysines, and histidines will be protonated, giving the peptide a net positive charge, since the pI of exendin-4 is 5.3. Thus, at such pH the bioactive peptide and cationic polyamino acid have the same net charge, and the claim is not unclear or indefinite.

35 U.S.C. 102

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631; 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

35 U.S.C. 102(a) over Rothbard

In the present case Rothbard does not disclose a composition where the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition. Rothbard explains at paragraph 44 (and 45) that the components of the composition (delivery-enhancing transporters such as poly-Arg (paragraph 48), and the biologically active agent (paragraph 26)) "are held in an ionic association, typically viewed as an ion pair." Thus, these components of an ion pair necessarily have opposite net charges at the pH of the composition, one net positive and the other net negative. Rothbard does not disclose or suggest a composition where the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition. Therefore, Rothbard does not disclose each and every element of the claim, and does not anticipate the present claims.

The rejection acknowledges that the components necessarily have opposite net charges at the pH of the composition (final Office Action mailed 2/2/09, p. 5, lines 7-9), then states that Rothbard meets "the limitation of neutral net charge". The rejection then proceeds to state that

"it is unclear how a peptide or protein of interest would have the same net charge as the cationic polyamino acid," and notes that if the cationic polyamino acid were a 13mer of poly-arginine, it would have a +13 charge, and that exendin-4 cannot have a +13 net charge.

But this reasoning of the rejection is legally erroneous. What is pertinent is whether or not Rothbard discloses each and every element of the claim, shown in as complete detail as the claim and arranged as in the claim. *Verdegaal Bros.* at 1053; *Richardson* at 1920; *In re Bond.* For the reasons already stated, this is not the case because Rothbard does not disclose a composition where the bioactive protein or peptide of interest has the same net charge as the cationic polyamino acid at the pH of the composition. Therefore, as a matter of law, the claim is not anticipated by Rothbard.

35 U.S.C. 102(e) over Defelippis and 35 U.S.C. 102(a) over Defelippis

Claims 1-4, 6-7, 9-10, 15-16, and 18-21 stand rejected under 35 U.S.C. § 102(a) and 35 U.S.C. § 102(e) as being anticipated by Defelippis et al. (WO 02/098348).

Defelippis discloses a composition comprising particles where the particles are comprised of a GLP-1 compound complexed with a basic polypeptide, such as polylysine, polyarginine, polyornithine or others (p. 5, lines 1-6).

The present claims recite that the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition. The disclosure of Defelippis makes it clear that the bioactive peptide or protein of interest and the cationic polyamino acid disclosed have opposite charges, and cannot have the same net charge. Defelippis et al. disclose that their formulation is comprised of particles of GLP-1 complexed with a basic polypeptide, such as polylysine, polyarginine, etc. Thus, the complex is present in a solid form and held together by an ionic bond. Therefore, it is necessarily is the case that the GLP-1 and polypeptide have opposite net charge, or they could not be held together in an ionic bond. This is even more clear with reference to Example 4 of Defelippis, where the pH of the composition is stated to be pH 9.2. At such pH, the GLP-1 has its charged amino acid residues present in de-protonated,

negatively charged form (e.g. the aspartic acids and glutamic acids, etc.). This too is made abundantly clear by Defelippis with reference to pp. 5-7, where many residues are made available to be present with a carboxyl group which is easily deprotonated at basic pH to provide a negatively charged peptide. Thus, Defelippis discloses a formulation where the bioactive peptide and the cationic polyamino acid (when present) have an opposite net charge and does not anticipate the presently claimed invention.

Furthermore, the present claims recite that the pharmaceutical composition has a pH at which the compatible buffer does not cause precipitation of the cationic polyamino acid. Defelippis discloses a composition at a pH where the GLP-1 and polyamino acid is precipitated, since it is disclosed as being in particle form (p. 5, lines 1-6; p. 41, Example 4), whereas the present claims require that the buffer "does not cause precipitation of the cationic polyamino acid." For this second and independent reason, the claims are not anticipated by Defelippis.

The rejection argues that Defelippis teaches a composition at the same pH comprising poly-arginine and exendin-4 and the use of acetate buffer. It then argues that since the composition has the same components as the claims, it inherently has the same functionality and characteristics of the claimed invention. (final Office Action mailed 2/20/09, p. 7, last paragraph). The logic of the rejection is legally and scientifically erroneous since it clearly is scientifically possible to have the same components arranged or present in different forms (consider diamonds v. graphite, both carbon). The Federal Circuit has stated that in order to anticipate, the elements must be arranged as required by the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236; 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The present claims recite that the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition, and that the compatible buffer does not cause precipitation of the cationic polyamino acid. What is legally relevant under the law of anticipation is whether or not Defelippis fulfills the requirements of the claims, which it does not for the reasons described above.

35 U.S.C. 103(a)

Claims 1-10 and 15-26 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Young (US 2003/0087820) in view of Baichwal (USP 5,330,761) and Ryser (USP 4,847,240).

To establish a prima facie case of obviousness it is necessary to consider whether there was an apparent reason to combine known elements in the manner set forth in the claim at issue, and this analysis should be made explicit *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398; 127 S. Ct. 1727 (2007). Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) (*quoted approvingly* in *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398; 127 S. Ct. 1727 (2007)).

One useful tool for assessing obviousness is to consider three basic criteria. First, whether there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, whether there is a reasonable expectation of success. Finally, whether the prior art reference (or references when combined) teaches or suggests all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *KSR v. Teleflex Inc.*; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142. "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006) MPEP 2143.01.

In the present case, Young discloses a liquid formulation comprising exendin, acetate buffer, mannitol as an iso-osmolality modifier (paragraphs 188-190 and 201). Young does not disclose a cationic polyamino acid at all, nor that the cationic polyamino acid has the same net charge as the peptide or protein of interest. Young is also directed to providing exendins and agonists to the blood plasma (paragraph 12) through various means. The liquid formulation of Young contains exendin, acetate buffer, mannitol, and optionally m-cresol (paragraph 201).

Baichwal is not properly combinable with Young. Baichwal discloses a tablet containing an active ingredient that is not absorbed into the body but instead provides a localized effect (Col. 2, lines 33-37), principally within the oral cavity (Col. 7, line 11). The solid dosage is comprised of a heterodisperse gum matrix that is bioadhesive when placed in contact with a mucous membrane (Col. 3, lines 21-24), such as the inside of the mouth. This formulation is disclosed as useful for locally administering anesthetics, antiseptics, anti-cariogenic or anti-plaque agents (Col. 10, examples 5-8).

Young functions according to a principle of utilizing a formulation to provide exendins to the blood plasma. Baichwal functions according to a principle of providing a solid tablet that is compressible (Col. 3, lines 21-24) and that is not absorbed into the body, but rather provides a localized effect (Col. 2, lines 33-37). Thus, modifying Young according to Baichwal changes the principle of operation of Young, and the two references are not properly combinable. MPEP 2143.01(VI).

Ryser is not combinable with Young either, because no motivation exists for doing so. Ryser discloses that the cellular uptake of some molecules could be improved by the simple presence in the experimental medium of cationic polymers (Col. 1, lines 51-56). Ryser make no disclosure on how to transport material across a mucous membrane to achieve transmucosal absorption. Rather, Ryser discloses that cellular uptake of some molecules could be improved by the presence of cationic polymers (Col. 1, line 55). Thus, Ryser is concerned with enhancing the cellular uptake of molecules that are either excluded from cells or taken up poorly by cells (Col. 3, lines 65-68). But Young is concerned with the introducing exendin into the blood plasma. Ryser is not relevant to the present invention, which recites a composition for transmucosal

administration of a bioactive peptide or protein, i.e., for transporting a peptide or protein across a mucosal membrane, such as the lining of the nasal passages or lungs. This is distinct from merely achieving a cellular uptake of a molecule as in Ryser. Thus, the person of ordinary skill finds no motivation to use a method to improve cellular uptake of a molecule in a composition for transporting exendin into blood plasma, as the two methods achieve introduction of the molecule into different biological structures. Thus, no rational underpinning is present for combining Ryser with Young.

Furthermore, Ryser is not properly combinable with Young for the additional reason that combining Ryser with Young changes the principle of operation of Young. Young functions on a principle of introducing the bioactive peptide exendin into the blood plasma for systemic administration (paragraphs 11 and 12) through various means. But Ryser functions according to a principle of cellular uptake through diffusion or active transport to achieve a localized affect, and not a systemic effect (Col 1, line 26). The person of ordinary skill in the art finds no reason that a method of increasing active transport or diffusion into a cell would have any effect on increasing the concentration of a peptide in the bloodstream. Modifying Young according to Ryser would therefore change the principle of operation of Young, and the two references are not properly combinable. MPEP 2143.01 VI.

For the same reason modifying Young according to Ryser would render Young unsatisfactory for its intended purpose (MPEP 2143.01 V), which is to introduce exendin into blood plasma. Thus for this additional and independent reason, Young is not properly combinable with Baichwal and Ryser.

The rejection appears to be based solely on impermissible hindsight and is made only by using the claims as a blueprint, and by selecting portions of the prior art to thereby form the rejection. But a properly formed rejection must be made without impermissible hindsight, and something in the prior art as a whole must suggest the desirability of making the combination. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044; 5 USPQ2d 1434 (Fed. Cir. 1988). Here, no rational underpinning to support the legal conclusion of obviousness has been made, and no apparent reason to combine the elements in the fashion claimed has been provided. Thus, no

prima facie case of obviousness has been made. *KSR Int'l Co. v. Teleflex Inc.* 550 U.S. 398 (2007).

For all of the above reasons, no prima facie case of obviousness has been made over the cited references.

Claims Appendix

1. A pharmaceutical composition for transmucosal administration of a bioactive peptide or protein of interest comprising said bioactive peptide or protein of interest, a cationic polyamino acid, and a compatible buffer, wherein at the pH of the composition said compatible buffer does not cause precipitation of the cationic polyamino acid, and has a mono-anionic or neutral net charge; and

wherein the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition; and

wherein the transmucosal absorption of said bioactive peptide or protein is increased relative the absorption of said bioactive peptide or protein in the absence of said cationic polyamino acid.

2. The composition of claim 1, wherein the pH of said composition is between about pH 4.0 and about pH 6.0.

3. The composition of claim 1, wherein the pH of said composition is between about pH 4.0 and pH 5.0.

4. The composition of claim 1, wherein said compatible buffer is selected from the group consisting of acetic acid, e-aminocaproic acid or glutamic acid.

5. The composition of claim 1, wherein said compatible buffer comprises glutamic acid.

6. The composition of claim 1, further comprising a tonicifying agent, a viscosity-increasing agent, a bio adhesive agent, a preservative, or any combination thereof.

7. The composition of claim 1, wherein said cationic polyamino acid comprises poly-histidine, poly-arginine, poly-lysine, or any combination thereof.

8. The composition of claim 7, wherein said cationic polyamino acid has an average molecular weight of between about 10 kDa and about 200 kDa.

9. The composition of claim 1, wherein said bioactive peptide or protein is an exendin, an exendin analog, or an exendin derivative.

10. The composition of claim 1, wherein said bioactive peptide or protein is selected from the group consisting of exendin-3, exendin-4, exendin-4 acid, exendin-4 (1-30), exendin-4 (1-30) amide, exendin-4 (1-28), exendin-4 (1-28) amide, ^{14}Leu, ^{25}Phe exendin-4 amide, and ^{14}Leu, ^{25}Phe exendin-4 (1-28) amide.

15. The composition of claim 6, wherein said tonicifying agent is selected from the group consisting of sodium chloride, mannitol, sucrose, glucose and any combination thereof.

16. The composition of claim 6, wherein said viscosity-increasing agent is selected from the group consisting of: hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose of average molecular weight between about 10 and about 1,500 kDa, starch, gums and any combination thereof.

17. The composition of claim 6, wherein said bioadhesive agent is selected from the group consisting of: carbomer, polycarbophil and any combination thereof.

18. The composition of claim 6, wherein said preservative is selected from the group consisting of phenylethyl alcohol, methylparaben, ethylparaben, propylparaben, butylparaben, chiorbutanol, benzoic acid, sorbic acid, phenol, m-cresol, alcohol, and any combination thereof.

19. The composition of claim 1, wherein said absorption is increased at least 2 fold.

20. The composition of claim 1, wherein said absorption is increased at least 5 fold.

21. The composition of claim 1, wherein said absorption is increased at least 10 fold.

22. A pharmaceutical composition for transmucosal administration of a bioactive peptide or protein of interest comprising about 0.01% to about 5.0% (w/v) of said bioactive peptide or protein of interest; about 0.01% to about 1.0% (w/v) of a cationic polyamino acid having a molecular weight between about 10 kDa and about 200 kDa; and about 0.01% to about 10.0%

(w/v) of a compatible buffer, wherein at a pH of between about pH 4.0 and about 5.0, said compatible buffer does not cause precipitation of the cationic polyamino acid and has a mono-anionic or neutral net charge; and wherein the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition, and wherein the transmucosal absorption of said bioactive peptide or protein is increased relative the absorption of said bioactive peptide or protein in the absence of said cationic polyamino acid.

23. The composition of claim 22, further comprising between about 0.001% to about 10.0% of a tonicifying agent.

24. The composition of claim 22, further comprising between about 0.001% to about 10.0% of a viscosity-increasing agent.

25. The composition of claim 22, further comprising between about 0.001% to about 10.0% of a bioadhesive agent.

26. The composition of claim 22, further comprising between about 0.001% to about 10.0% of a preservative.

27. A pharmaceutical composition for transmucosal administration comprising about 0.5% (w/v) of exendin-4; about 0.5% (w/v) of poly-arginine having an average molecular weight of about 141 kDa; and about 0.56% monosodium glutamate monohydrate (w/v), at a pH of about 4.5 and wherein the exendin-4 has the same net charge as the poly-arginine at the pH of the composition.

28. The composition of claim 27, wherein said poly-arginine is poly-L-arginine.

29. The composition of claim 27, wherein said composition further comprises a tonicifying agent, a viscosity-increasing agent, a bioadhesive agent, a preservative, or any combination thereof.

30. The composition of claim 27, further comprising about 0.72% sodium chloride (w/v).

31. A pharmaceutical composition for transmucosal administration comprising about 0.5% (w/v) of exendin-4; about 1.0% (w/v) of poly-arginine having an average molecular weight of about 141 kDa; and about 0.56% monosodium glutamate monohydrate (w/v), at a pH of about 4.5 and wherein the exendin-4 has the same net charge as the poly-arginine at the pH of the composition.

32. The composition of claim 31, wherein said poly-arginine is poly-L-arginine.

33. The composition of claims 31, wherein said composition further comprises a tonicifying agent, a viscosity-increasing agent, a bioadhesive agent, a preservative, or any combination thereof.

34. The composition of claim 31, further comprising about 0.72% sodium chloride (w/v).

Evidence Appendix

None

Related Proceedings Appendix

None

Closing

In view of the above the Applicant respectfully requests that the rejections be reversed and that the claims be passed to allowance (or examination continued beyond the elected species).

No fees are believed due with this filing because the Applicant previously paid both the Notice of Appeal and Appeal Brief fees under 37 CFR 41.20(b)(1) and (b)(2) on April 11, 2008, and having been once paid are not further due (MPEP 1204.01). However, if Applicant is in error and any fees are due, the USPTO is authorized to debit PTO Deposit Account # 01-0535 for said fees, as well as to credit back any refunds or overcharges.

Respectfully submitted

July 17, 2009
Date

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